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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,494	09/29/2005	David Cheshire	06275-469US1 100905-1P US	4625

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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,494	CHESHIRE ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Applicant's Remarks filed 9/29/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 13-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I with R4 and R5 or R6 and R7 as claimed other than joining together to represent a C3 to 6 cycloalkyl, does not reasonably provide enablement for using the compounds with R4 and R5 or R6 and R7 coming together to form a C3 to 6 cycloalkyl. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In

re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining if any particular claimed compounds with R4 and R5 or R6 and R7 coming together to form a C3 to 6 cycloalkyl would be active would require synthesis of the substrate and subjecting it to testing with Applicants' inhibition of NO synthase assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 15-28 which merely states Applicants' intent to make and use such compounds. c) In the instant case, none of the working examples contains any radical with R4 and R5 or R6 and R7 coming together to form a C3 to 6 cycloalkyl. d) The nature of the invention is inhibition of NO synthase and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the NOS receptor, the binding activity of small ligands to that receptor, and the ability of those compounds to inhibit NOS. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these

claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) There is no reasonable basis for the assumption that the myriad of compounds embraced by the present formula (I) will all share the same biological properties. The diverse claimed compounds are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the

potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various radicals, which are not art-recognized as equivalent. The specific

compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-14, 16, 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some inflammatory diseases and some disease conditions in which inhibition of nitric oxide synthase activity is beneficial, does not reasonably provide enablement for treating all of these diseases or reducing the risk of any of these diseases or prophylaxis of all inflammatory disease. It is not established in the art to prevent any inflammatory

disease or to reduce the risk of any of these diseases in humans. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The main issues are the correlation between clinical efficacy for treatment, prophylaxis and reducing the risk of the diseases noted above and Applicants' NOS inhibition assay.

a) Determining if any particular claimed compound would treat, prevent, or reduce the any particular inflammatory disease or any disease in which inhibiting nitric oxide synthase activity is beneficial, would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment.

This is a large quantity of experimentation. b) The direction concerning treating, prophylaxis, or reducing the risk of the claimed diseases is found at page 12, lines 13-28 and at page 13, lines 13-32, which merely states Applicants' intention to do so. Applicants describe formulations at page 14, lines 11-20. Doses required to practice their invention are described in line 9, page 14. A 2000-fold range of doses is recommended. Since these compounds have never been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are no guidelines for determining the doses needed to provide a NOS inhibitory effect. Are identical doses to be used for treating these unrelated diseases? There is an NOS inhibitory assay described in lines 10-30 at page 29 and page 30, with no data specifically and separately recited for each of the examples 1 to 10 tested - it is unclear if this assay is correlated to the treatment or prophylaxis or reducing the risk of the diseases claimed. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment, prophylaxis and reducing the risk of the claimed disease with applicant's compounds which involves physiological activity. e) The state of the clinical arts is that large amounts of nitric oxide are produced at sites of inflammation through the action of inducible nitric oxide synthase present in both infiltrating leukocytes and activated resident tissue cells. See Hcaplus

124:171796. However, the role of NO in inflammation remains unclear. See Hcaplus 124:171796. The state of the art provides contradictory information on the effect of NO on vascular leakiness, chemotaxis, prostaglandin production and tissue damage. See Hcaplus 124:171796. Increasingly, data suggest that NO is immunosuppressive. See Hcaplus 124:171796. Inhibitors of NOS have been stated to have potent prophylactic activity in several but not all, animal models of inflammatory disease. However, in rat adjuvant arthritis, therapeutic activity is weak. See Hcaplus 124:171796. Whether inhibitors of iNOS will be therapeutically useful in human inflammatory disease cannot be predicted on the basis of present information. See Hcaplus 124:171796.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably

predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the thousands of compounds of claim 13 as well as the hundreds of diseases embraced by the phrase " disease or condition in which inhibition of nitric oxide synthase activity is beneficial" and "inflammatory disease". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 13-20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 6-15 of copending Application No. 10551495.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches a subgenus of compounds, a method of using these compounds to treat inflammatory diseases and conditions and diseases in which inhibition of nitric oxide synthase is beneficial and a method of preparing the subgenus of compounds by reacting a compound of formula IV with a compound of formula VII and converting the resultant compound to a compound of formula I.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The copending application teaches the subgenus of compounds of formula I, a method of using these compounds to treat, prevent, or reduce the risk of inflammatory diseases and conditions and diseases in which inhibition of nitric oxide synthase is beneficial and a method of preparing the subgenus of compounds by reacting a compound of formula IV with a compound of formula VII and converting the resultant compound to a compound of formula I. See the subgenus of formula I at claim 1 and see claim 15, and claim s 6 and 8. The difference between the prior art subgenus, method of treating with this subgenus and method of preparing this subgenus and the instantly claimed genus, method of treating with this genus, and method of preparing with this genus – is the L1 group which in the subgenus cannot represent a bond, whereas in the instant genus L1 can represent a bond . It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. Accordingly, the compounds, compositions, methods of treating and methods of manufacture are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds, uses, and methods of manufacture over those of the generic prior art compounds, uses and methods of manufacture.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Janet Andres can be reached on 571-272-0867.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

Brita Robinson

BMR
January 17, 2008

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER